Causal Inference

2004 Epidemiology, Biostatistics and Clinical Research Methods Summer Session

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Part 7

Principles Underlying Causal Inference

- Association versus causation
- Criteria for formulating a plausible causal hypothesis, based on results of
  - Randomized trials
  - Nonrandomized studies
- Putting the criteria to use in specific situations

Why Epidemiologists?

- Society employs epidemiologists to provide input for decisions regarding disease and injury prevention

Decisions About Prevention

- For oneself
- For one's patients
- Collectively, by society as a whole

Association of Disease With an Exposure

- The frequency of disease differs according to the presence (or level) of the exposure
- The difference in frequency of disease may or may not be due to the action of the exposure itself

Cause of a Disease

- An exposure or characteristic whose presence has led to one or more individuals developing the disease

Fertility Drugs and Tumor Risk

- Women who undergo long-term treatment with fertility drugs have an elevated risk of developing an ovarian tumor
- Could this be due to the drugs themselves?
  - The abnormal hormonal milieu present in some infertile women?
  - Infertile women having fewer term pregnancies than other women?

Association vs. Causation

- Associations are “observed”
- Causes are “inferred”

What Impairs Inferences Regarding Disease Causation?

- A lengthy interval between the presence of the causal factor and the manifestation of its effect
- The same effect can occur due to the action of other causes
- The causal factor requires the presence of other factors to produce the effect

Criteria Used to Form Plausible Causal Hypotheses

- Data from randomized studies in human beings show an association

Randomized Studies

- In these studies, chance alone dictates which participants of the study are exposed
  - Therefore, other factors that influence the risk of disease or injury generally will not distort the results
- It is not feasible, however, to study all etiologic questions with randomized trials, and it is not ethical to use this design to study some others

Criteria Used to Form Plausible Causal Hypotheses

- Data from nonrandomized studies in human beings show an association and
  - Suspected cause precedes disease
  - Association is strong
  - No likely noncausal basis for the association
  - Association makes biological sense
  - Magnitude of association is strongest when predicted to be so

Criterion for a Strong Association

	Illness A	Total	Illness B	Total
Exposed	10	100	55	100
Nonexposed	1	100	46	100
Risk ratio (relative risk)		10		1.2
Risk difference		9/100		9/100

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HIV Transmission

In couples discordant for HIV infection, does condom use protect against HIV transmission?

	HIV status at end of 20 months of follow-up	
Condom use	Infected	Uninfected
Consistent	0	124
Inconsistent or none	12	109

Reference: NEJM 1994;332:341-6

Reason for Low HIV Incidence?

Among HIV discordant couples, is something different about consistent condom users that might explain their low incidence of transmission?

	Consistent users n=124	Others n=121
Median follow-up duration	22 months	23 months
Male as index partner	67%	61%
Frequency of sexual contact during follow-up	Twice per week	Once per week

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Do French Fries Cause Cancer?

According to Swedish researchers, frying potatoes or other starchy foods triggers the formation of an organic molecule called acrylamide, which has been shown to cause cancer in laboratory rats.

Time Magazine
May 2, 2002

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Cigarette Smoking and Lung Cancer in Men

Cigarettes smoked per day	Annual death rate per 100,000	Relative lung cancer mortality
Never smoked	12	1.0
1-9	56	4.6
10-19	90	7.5
20-39	159	13.1
40+	201	16.6

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Menopausal Estrogen Use in Women with Endometrial Cancer and Controls

Years since first use	Relative risk	95% confidence interval
Never used	1.0	—
1-2	1.2	0.4-3.7
3-4	5.4	2.5-11.5
5-7	4.7	2.6-8.4
8-10	11.7	6.2-21.8

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Implementation of Causal Criteria

- Arriving at a tentative inference (always pending the arrival of new data) of “causal” or “noncausal” is a subjective process in which one judges how well the individual criteria have been fulfilled

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Review of Concepts of Causation

1. Do we care if an exposure produces disease “directly” or “indirectly?”

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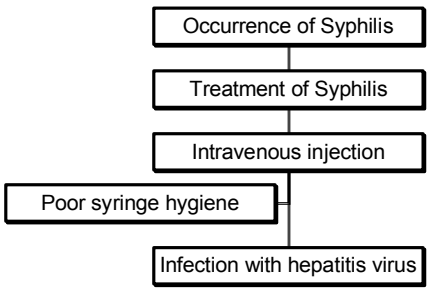
One Causal Pathway Leading to Hepatitis in the 1930s



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Review of Concepts of Causation

2. In order to be considered causal, must the exposure have been present in all persons with the disease?
   (What happened to Koch's postulates?)

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Review of Concepts of Causation

3. In order to be considered causal, must the exposure be capable of producing the disease on its own?

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Do guns kill people? or Do people kill people?

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Guns and Homocide

- A gun by itself does not commit a homicide
- Does that detract from the inference that the availability of a gun is a cause of homicide?

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Action Following Causal Inference?

- Following an inference of cause and effect, it may or may not be appropriate to take preventive action

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Sudden Infant Death Syndrome in Relation to Sleeping Position

Study location	Cases	Information obtained before or after death	Usual or last	RR*
Holland	62	After	Usual	9.3
			Last	4.9
U.K.	72	After	Last	8.8
N.Z.	473	After	?	3.3
Australia	42	After	Usual	3.5
	15	Before	Usual	4.5

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Evaluation of the impact of the UK "Back to Sleep" campaign which began 12/91

Year	% newborns in prone position	# SIDS deaths
1991	21%	912
1992	4%	456

Reference: BMJ 1994;309:703-4

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Hepatocellular Carcinoma and Hepatitis B Virus

- Primary hepatocellular carcinoma (PHC) is the most common malignant neoplasm in much of Asia and Africa

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Hepatocellular Carcinoma and Hepatitis B Virus

- By 1980, several types of evidence pointed to a possible etiologic role of infection with hepatitis B virus:
  1) There was a strong correlation between prevalence of hepatitis B infection in a. population (as measured by the presence of hepatitis B surface antigen (HBsAg) in serum) and that population's mortality rate from PHC
  2) In several studies, HBsAg was detected more commonly in serum of patients with PHC than in serum from controls

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Hepatocellular Carcinoma and Hepatitis B Virus

- To further assess whether the HBsAg carrier state predisposes to the development of PHC, a prospective study was done among Chinese male civil servants in Taiwan.
- A total of 22,707 men were recruited into the study during 1975-78, and followed for mortality until the end of 1980.

Deaths by Cause and HBsAg Status on Recruitment

HBsAg status on recruitment	Cause of death			Population at risk	PHC incidence*
	PHC	Cirrhosis	Other		
HBsAg-positive	40	17	48	3454	1158
HBsAg-negative	1	2	199	19.253	5
Total	41	19	247	22.707	181

* Incidence of death from PHC per 100,000 during the time of the study

Lancet 1981;2:1129-33

PHC Incidence and Length of Follow-up

Year of follow-up	HBsAg-positive		PHC incidence*
	Men in follow-up	PHC deaths	
1	3454	15	434
2	3426	11	321
3	3397	7	206
4	2275	6	264
5	309	1	324

* Incidence of death from PHC per 100,000 during the time of the study

Lancet 1981;2:1129-33

Hepatocellular Carcinoma and Hepatitis B Virus

- The authors concluded that "This study shows that the risk of PHC is much higher in HBsAg carriers than in noncarriers.“
- They went on to say that "Although this study strengthens the argument that HBV may be a cause of PHC, it does not prove it. Alternative explanations of the very high relative risk among. HBsAg carriers are that ·the HBV is a cofactor with another etiologic agent or is simply a risk factor."

Hepatocellular Carcinoma and Hepatitis B Virus

- Based on the above information, do you believe it is reasonable to infer that infection with hepatitis B virus is a cause of primary hepatocellular carcinoma?
- If yes, why?
- If no, why not?